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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/632,095	08/01/2003	David Hone	08560002AA	1913

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EXAMINER	
LIETO, LOUIS D	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/632,095	HONE, DAVID	
	Examiner	Art Unit	
	Louis D. Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 17-20* is/are pending in the application.

4a) Of the above claim(s) *3,4 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-14 and 17-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 3/21/2005 is acknowledged. . Claims 1-15, 17-20 are pending. Claims 1,2,5-14 and 17 have been amended, claim 16 has been cancelled. This application contains claims 3,4 and 15 drawn to an invention nonelected without traverse in the action mailed on 11/03/2004. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1, 2,5-14 and 17-20 are under consideration. The sections of 35 U.S.C. not included in this office action can be found in a previous office action. An action on the merits follows.

Priority

The objection over applicant's failure to properly claim priority to a previously filed application is withdrawn in view of applicant's amendment to the specification.

Specification

The objection to the specification because of an improper attempt to incorporate subject matter into this application by reference to the "Appendix" is withdrawn in view of applicant's amendment to the specification.

Claim Rejections - 35 USC § 112

Claims 1,2,5-14 and 17 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record set forth in the previous office action of 11/3/2004. Claim 16 has been cancelled, and claims 3,4 and 15 have been withdrawn. While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided.

The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not reasonably provide enablement for a DNA vaccine comprising at least one genetic sequence encoding a mART derived from cholera toxin containing the L41F mutation, and at least one genetic sequence encoding an antigen; and a method of vaccinating a patient with the DNA vaccine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to perform the invention commensurate in scope with these claims.

The 1.132 declaration by Dr. David Hone, filed on 3/03/2005 is acknowledged.

Response to Arguments

Applicant's arguments filed 3/21/2005 have been fully considered but they are not persuasive. The previous office action identified the following issues of record: **1)** lack of enablement for a DNA vaccine comprising any and all variants, mutants and fragments of mART derived from cholera toxin, as long as the mART includes a L41F mutation; **2)** lack of an enabling disclosure on how to predict which single amino acid mutations of the A1 subunit of

CT render it non-toxic yet immunogenic; **3)** lack of an enablement of a DNA vaccine comprising a genetic sequence encoding a mART derived from cholera toxin containing a L41F mutation and a genetic sequence encoding an antigen; and **4)** lack of enablement for using any expression vector/promoter combination to express a DNA vaccine comprising a genetic sequence encoding a mART derived from cholera toxin containing a L41F mutation and a genetic sequence encoding an antigen *in vivo*.

1) Applicant has amended the claims so that the invention now reads on a composition for eliciting an immune response, instead of a DNA vaccine. However, the sole disclosed utility of the invention in the Specification is as a DNA vaccine (Specification, pg.6 lines 15-22). Further, the amended language of claim one drawn "eliciting an immune response" is consistent with the disclosed utility. Therefore, demonstration of an immune response does not provide enablement for the intended use of the invention as a DNA vaccine. Finally, applicant provides a 1.132 declaration by Dr. David Hone, filed on 3/03/2005. However, even though the declaration purports to demonstrate the ability of genes encoding an L41F mutant cholera toxin and an antigen to elicit an immune response it does not do so. As stated on page 3 of the declaration (line 1 & 2) only "the adjuvant activity of DNA vaccines that encode S63Y and S41Y derivatives of CtxA1" was tested. Further, despite applicant's contention in the response (pg. 7, pgph 2) the L41F mutation is not the same as CtxA1 S41Y. The single letter nomenclature of amino acids is well established. Applicants elected the species of L41F, which means that the DNA encoding the Leucine at position 41 was mutated to encode Phenylalanine. L41F has a fixed meaning in the art and can never be interpreted to mean S41Y. S41Y has its own separate and distinct meaning, that the DNA encoding a Serine at position 41was mutated to encode a Tyrosine. The

declaration is considered to be irrelevant to the issues of enablement in the instant case. For the reasons of record stated in the previous action the rejection over issue **1** is maintained.

2) Applicant next argues that the declaration answers the examiners concerns about the toxicity of the composition. However as noted above the declaration does not address the enablement issue raised. For the reasons of record stated in the previous action the rejection over issue **2** is maintained.

3) Applicant argues that the declaration demonstrates that at least one genetic sequence encoding a mART with the L41F mutation can induce an immune response. However as noted above the declaration is irrelevant since it does not describe any data with a mART containing the L41F mutation. For the reasons of record stated in the previous action the rejection over issue **3** is maintained.

4) Applicant argues that one of skill in the art would expect that vectors other than a plasmid would be equally successful when used in the composition. However other than their assertions, applicant does not provide any supporting evidence for their position, such as a relevant declaration, supporting references or by addressing the substance of the rejection stated in the previous office action of 11/03/2004. As was previously stated:

The specification also does not provide an enabling disclosure for using any expression vector/promoter combination to express a DNA vaccine comprising a genetic sequence encoding a mART derived from cholera toxin containing a L41F mutation and a genetic sequence encoding an antigen *in vivo*. The claims read on any vectors, including plasmids, viral vectors, retroviral vectors, naked DNA and naked RNA. The claims also read on any promoters, including SV40, CMV, or SV2. Verma et al. states that, the Achilles heel of gene therapy is gene

delivery, and that, most of the approaches suffer from poor efficiency of delivery and transient expression of the gene {Verma et al. (1997) Nature, Vol. 389, page 239, col. 3, pgph 2}. Marshall concurs, stating that, difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field, and that, many problems must be solved before gene therapy will be useful for more than the rare application {Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1}. Orkin et al. further states in a report to the NIH that, none of the available vector systems are entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated, and that, while the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol {Orkin et al. (1995) Report and recommendations of the panel to assess the NIH investment in research on gene therapy, page 1, paragraph 3, and page 8, paragraph 2}. Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are anti-viral immune responses, and the need for appropriate vector/promoter combinations for a particular cell type. In regards to the latter issue, Verma states that, the search for such combinations is a case of trail and error for a given cell type {Verma, (1997) Nature, 389, page 240}. Thus, given the lack of guidance in the specification on how to construct any vector with any promoter or promoters comprising a DNA vaccine comprising a genetic sequence encoding a mART derived from cholera toxin containing a L41F mutation and a genetic sequence encoding an antigen, a skilled artisan would be unable to practice the invention, except with a DNA plasmid containing the CMV promoter for *in vivo* transfection, without arduous and undue experimentation.

Applicant has not provided any evidence or references supporting their contention that any vector would be reasonably expected to succeed. Further, as stated previously: the working examples only describe two vectors that comprise a genetically encoded mART and an antigen: 1) pCtxA1-E29H (with the CMV promoter), which comprises genetic sequences of the E29H mART and the receptor binding domain of protective antigen of *Bacillus anthracis*; 2) pOGL1-A1-S63K (with the CMV promoter), which comprises genetic sequences of the S63K mART and gp120. The specification does not provide any basis for comparing the activity of a composition, intended for use as a DNA vaccine, comprising S63K mART and gp120 with a composition, intended for use as a DNA vaccine, comprising L41F mART and any antigen. For the reasons of record stated in the previous action the rejection over issue **4** is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 2 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Hase et al. { Hase et al. (1994) Infection and Immunity. 62:3051-3057}. This rejection is necessitated by applicant's amendments to the claims. Specifically, the claims now read on a "composition", which encompasses a cell comprising the claimed genetic sequences.

Hase et al. provides guidance on the creation of a mutant CT-A (mART) plasmid that encodes a protein lacking ADP-ribosylation activity because of codon substitutions (Abstract). Further, Hase et al. teaches transforming *V. cholerae* strain JBK70 with the plasmid encoding the mutant mART, a plasmid containing a mutant *zot* toxin gene, and a plasmid containing a mutant CT-1 gene, both of which produce antibodies (Abstract; pg. 3052, Materials and Methods). Finally, Hase et al. provides guidance that the transformed *V. cholerae* strain can be used as an attenuated live vaccine. Therefore, the disclosure of Hase et al. meets all of the limitations of the above rejected claims.

No claims allowed

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-272-0735. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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